IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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6/14/03

Application of:	ALLEN et al.	Group Art Unit:	1636
Serial No.:	09/815,825	Examiner:	Daniel M. Sullivan
Filed:	March 22, 2001	Attorney Dkt.:	R-849
For:	TRANSGENIC MICE CONTAINING cGMP PHOSPHODIESTERASE GENE DISRUPTIONS		

RESPONSE UNDER 37 CFR § 1.111

Mail Stop Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This amendment is responsive to the Office Action dated December 2, 2002, for which a three-month period for response was given making this response due on or before March 2, 2003. Applicants submit concurrently herewith a Petition for an Extension of Time under 37 CFR § 1.136(a) for response to the Office Action for a period of three (3) months from March 2, 2003 up to and including June 2, 2003. Additionally, Applicants make note that this response is submitted in the revised format as described in a Pre-OG notice titled, "*AMENDMENTS IN A REVISED FORMAT NOW PERMITTED*," signed January 31, 2003, published in the *Official Gazette* on February 25, 2003. As such, only one copy of each replacement paragraph, section or claim is required.

In view of the amendments to the claims and the remarks put forth below, reconsideration and allowance are respectfully requested.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,825	03/22/2001	Keith D. Allen	R-849	6413

26619 7590 12/02/2002

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EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

RESPDE 3.2.03

Office Action Summary	Application No.	Applicant(s)	
	09/815,825	ALLEN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-14,17-23,26-33,35,37,39,42 and 45-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *8,17-19,21 and 42* is/are allowed.

6)☒ Claim(s) *1-5,9-14,20,22,23,26-33,35,37,39 and 45-47* is/are rejected.

7)☒ Claim(s) *27-31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 September 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Non-Final Office Action is a response to the Response under 37 CFR § 1.111 filed September 13, 2002 (Paper No. 13) in reply to the Office Action mailed March 13, 2002 (Paper No. 11). Claims 6, 7, 15, 16, 24, 25, 34, 36, 38, 40, 41, 43, 44 and 48 were cancelled and claims 1-5, 8-14, 17-23, 26-33, 35, 37 and 39-47 were amended in Paper No. 13. Claims 1-5, 8-14, 17-23, 26-33, 35, 37, 39, 42 and 45-47 are pending and under consideration in the application.

Drawings

The corrected or substitute drawings were received on September 13, 2002. These drawings are acceptable.

Response to Amendment

Claims 6, 7, 15, 16, 24, 25, 34, 36, 38, 40, 41, 43, 44 and 48 have been cancelled. All rejections and objections, as they pertain to the cancelled claims, have thereby been rendered moot.

Claim Rejections - 35 USC § 112, First Paragraph (enablement)

Rejection of claims 8, 9, 11, 17-23, 26, 35, 37, 39 and 42 under 35 USC 112, first paragraph, as lacking enablement commensurate with the full scope of the claims, for reasons of record in Paper No. 11, is withdrawn in view of the amendments to the claims such that the scope of the claims is now limited to transgenic mice comprising a disruption in a cGMP

phosphodiesterase alpha subunit gene, embodiments that are fully enabled according to the requirements of 35 U.S.C. § 112, first paragraph.

Claims 1-5, 10, 12-14, 27-33 and 45-47 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claims for reasons of record in Paper No. 11.

With regard to claims 1-5 and 10, in response to the rejection, Applicant has amended the claims such that they are now directed to a murine targeting construct, method of producing a murine targeting construct and method of using a murine targeting construct. Applicant submits that the rejections are overcome by the amendments. However, the amended claims encompass rat as well as mouse targeting constructs and are therefore still directed to subject matter that is not enabled by the disclosure (i.e. rat targeting constructs) for the reasons provided in Paper No. 11.

With regard to claims 10, 12-14, 27-33 and 45-47, the scope of the claimed subject matter is still beyond what is enabled by the disclosure because the claims fail to properly limit the knockout mouse to a mouse that exhibits a phenotype that the skilled artisan would know how to use. For example: the mouse of claims 10 and 12-14 are not limited to any phenotype at all; although the preamble of claim 33 indicates that the claim is directed to a method of identifying an agent which modulates a phenotype comprising an eye abnormality, the mouse of step (a) is not limited to a mouse having an eye abnormality; likewise, the mouse in step (a) of claims 45-47 is not limited to a mouse having a hyperactive phenotype.

Claim Rejections - 35 USC § 112, First Paragraph (possession)

Rejection of claims 8, 11, 17-23, 26, 35, 37 and 42-44 under 35 U.S.C. § 112, first paragraph, as lacking adequate written description, for the reasons of record in Paper No. 11, is withdrawn in view of the amendments to the claims such that they are now directed to transgenic mice comprising a homozygous disruption of in a cGMP phosphodiesterase alpha subunit gene and a defined phenotype.

Claims 12, 27-33, and 45-47 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking written description for any and all knockout mice comprising an altered allele for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase. As described herein above under 35 U.S.C. § 112, first paragraph (enablement), the rejected claims fail to limit the knockout mouse to a mouse expressing a phenotype that was described in the disclosure. According to the definition of "disruption" in the second paragraph on page 7 of the specification, the claims encompass mice having insertions, missense, frameshift, deletion, substitution or replacement modifications of the cGMP phosphodiesterase alpha subunit gene. The claims therefore encompass a genus of mice having a variety of genotypes, which could give rise to various phenotypes depending on whether the cGMP phosphodiesterase is absent or present in some modified form. As pointed out in Paper No. 11, Applicant has only described mice having a homozygous disruption of the cGMP phosphodiesterase alpha subunit gene and a phenotype of eye abnormality or hyperactivity. Therefore, for the reasons of record in Paper No. 11, the skilled artisan would not have viewed the teachings of the specification as sufficient to show that Applicant was in possession of the claimed invention commensurate to its scope.

Claim Rejections - 35 USC § 112, Second Paragraph

Rejection of claim 1 under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps is withdrawn in view of the amendment of the claim such that the process steps are properly labeled.

Claim Rejections - 35 USC § 103

Rejection of claims 1-5, 8-14, 17-23, 26-33, 37 and 39-47 under 35 U.S.C. § 103 as being unpatentable over Baehr *et al.*, and Lem *et al.* and in further view of Tanabe *et al.* for reasons of record in Paper No. 11 is withdrawn in view of the amendments to the claims such that they are now limited to: targeting constructs comprising sequence homologous to the cGMP alpha subunit gene; cells comprising disruption in a cGMP phosphodiesterase alpha subunit gene; transgenic mice comprising homozygous disruption in a cGMP phosphodiesterase alpha subunit gene and having the phenotype comprising an eye abnormality; and methods of using said targeting constructs, cells and transgenic mice. None of the art cited in the Office Action contemplates transgenic mice comprising a disruption in the cGMP phosphodiesterase alpha subunit. Given the unpredictability of phenotype associated with disruption of any given gene in a transgenic animal, a use for the targeting constructs, cells, animals and methods of the instant invention would not have been obvious to the ordinary skilled artisan at the time the invention was made based on the teachings of the prior art.

Claim 35 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Baehr *et al.* and Lem *et al.* and in further view of Tanabe *et al.* for reasons of record on Paper No. 11. In response to the rejection, Applicant has amended the claim such that it is directed to a method of using a mouse comprising a homozygous disruption in a cGMP phosphodiesterase gene, wherein said mouse exhibits an eye abnormality. The amended claim is still unpatentable over the cited art, which, as described in Paper No. 11, also describes mice having homozygous disruption of cGMP phosphodiesterase beta and gamma subunits, and expressing eye abnormalities.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 23 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing a transgenic mouse comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene and exhibiting an eye abnormality or hyperactivity, comprising introducing a cGMP phosphodiesterase alpha subunit gene targeting construct into a mouse ES cell, and a cell isolated from the transgenic mouse produced according to the method, does not reasonably provide enablement for a method, or cell isolated from an animal produced by the method, wherein a transgenic mouse is produced from any cell other than an ES cell. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims.

The claims encompasses methods of making transgenic mice comprising: introducing a targeting construct into any cell; introducing said cell into a blastocyst; implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and breeding the chimeric mouse to produce the transgenic mouse. To date, the relevant art only teaches production of knockout mice using ES cells (see Campbell *et al.* (1997) *Theriogenology* 47:63-72 (cited in Paper No. 11)). The prior art does not provide a single example of a knockout animal being produced from any cell other than an ES cell; therefore the skilled artisan must depend upon the teachings of the instant disclosure to provided detailed guidance as to how to make the invention using other cell types. The specification is silent, however, with respect to how to make a knockout animal using any cell other than a mouse ES cell. Although the relative level of skill in the art is high, because neither the prior art nor the instant disclosure provide any guidance as to how to produce a knockout mouse from a cell other than an ES cell, the skilled artisan would not know how to make a knockout mouse using any cell other than an ES cell. One of ordinary skill in the art would therefore have to engage in undue experimentation in order to develop methods of producing a knockout mouse from a cell other than an ES cell.

Claims 11-14, 32, 37, 39 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of identifying an agent that modulates the expression or function of a cGMP phosphodiesterase or phosphodiesterase gene in a transgenic animal comprising a homozygous disruption in the cGMP phosphodiesterase gene. According to the teachings of the specification, the transgenic animal comprising a homozygous disruption in the cGMP phosphodiesterase gene will no longer comprise cGMP phosphodiesterase. The skilled artisan would not predict that it would be possible to assess modulation or function of cGMP phosphodiesterase in a transgenic animal comprising a homozygous disruption in a cGMP phosphodiesterase gene because the animal would not express a measurable gene product. The skilled artisan would not be able to practice the claimed invention without undue experimentation because the techniques standard in the art and disclosed in the specification do not enable the skilled artisan to measure expression or function of a gene product that is not present.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 20, 22, 26, 33 and 45-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in reciting a limitation as a derivative of some starting material (i.e. a cell derived from a transgenic mouse). Without a clear statement of the process by which

the starting material is derivatized it is not possible to know the metes and bounds of such a limitation because any given starting material can have many divergent derivatives depending on the process of derivatization. It would appear that Applicant intends that cell merely be obtained or isolated from the transgenic animal and amending the claim accordingly would obviate this rejection.

Claim 20 is indefinite in that it fails to further limit claim 18, from which it depends. Claim 18 is directed to a transgenic mouse having a retinal degeneration or dysplasia, while claim 20 is directed to any eye abnormality that is consistent with vision problems or blindness. This rejection could be traversed by amending claim 20 such that it depends from claim 8 or 17.

Likewise, claim 22 is indefinite in being directed to a variety of eye abnormalities while claim 17, from which claim 22 depends, is limited to a retinal abnormality.

With regard to claims 27, 28-31 as they depend from 27, 33 and 45-47, each of the claims is indefinite in being directed to a method of measuring an alteration in a phenotype in a transgenic mouse, wherein the transgenic mouse is not limited to a mouse having the measured phenotype. For example, claims 27 and 33 are directed to identifying an agent that ameliorates or modulates an eye abnormality but the mouse used in step (a) is not limited to a mouse having an eye abnormality. Likewise, claims 45-47 are directed to methods comprising determining hyperactive behavior in a mouse but the mouse is not limited to a mouse having hyperactive behavior.

Claim Objections

Claim 27, and 28-31 as they depend from claim 27, are objected to because of the following informalities: there is a typographical error in line 4 (i.e. two semicolons following the word "gene"). Applicant is urged to carefully review the disclosure and correct any errors in the text. Appropriate correction is required.

Allowable Subject Matter

Claims 8, 17-19, 21 and 42 are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
November 29, 2002

ANNE-MARIE BAKER
PATENT EXAMINER